UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Triethanolamine complex of copper (K-TEA Technical): Review of 4 toxicity studies submitted by the registrant on the acute oral toxicity (81-1), the acute dermal toxicity (81-2), the primary eye irritation (81-4) and the primary dermal irritation (81-5) of K-TEA Technical.

Caswell No.: 257BB
HED Project No.: 2-0526
MRID Nos: 417593-01, -02, -03, -04.

FROM: Walter J. Kozumbo, Ph.D., Toxicologist W. Kozumbo 2-11-92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Barbara Briscoe/Kathryn Davis, PM Team 51
Special Review and Reregistration Division
(H7508W)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y.M. Ioannou 2/11/92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) Marcia Van Gemert 2/12/92

REGISTRANT: Griffin Corporation

ACTION REQUESTED: For reregistration purposes, evaluate studies on K-TEA Technical to determine its acute oral and acute dermal toxicities as well as its potential to irritate eyes and skin according to FIFRA guidelines 81-1, 81-2, 81-4 and 81-5, respectively.

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CONCLUSIONS:

1. Acute Oral in Rats (81-1) (MRID # 417593-01): The LD50s for K-TEA Technical in rats were determined to be 1170 mg/kg for males, 1481 mg/kg for females, and 1312 mg/kg for both sexes combined. This study does not satisfy guideline requirements (81-1) for an acute oral toxicity study. Upgrading is possible, however, upon the submission and favorable review of chemical analytical data establishing purity of the test article at the time of animal treatment. Toxicity Category III.

2. Acute Dermal Toxicity in Rabbits (81-2) (MRID # 417593-02): A single topical application of K-TEA Technical at a limit-test dose of 2000 mg/kg to rabbits (5 per sex) for 24 h resulted in no deaths after 15 days of observation. The acute dermal LD50 in rabbits was therefore determined to be > 2000 mg/kg. This study does not satisfy guideline requirements (81-2) for an acute dermal toxicity study. Upgrading is possible, however, upon the submission and favorable review of chemical analytical data establishing purity of the test article at the time of animal treatment. Toxicity Category III.

3. Primary Eye Irritation in Rabbits (81-4) (MRID # 417593-03: K-TEA Technical caused moderate irritations of the cornea, iris and conjunctiva that were resolved within 7 days. This study does not satisfy guideline requirements (81-4) for a primary eye irritation study. Upgrading is possible, however, upon the submission and favorable review of chemical analytical data establishing purity of the test article at the time of animal treatment. Toxicity Category III.

4. Primary Dermal Irritation in Rabbits (81-5) (MRID # 417593-04): When applied to the skin of rabbits, K-TEA Technical produced mild irritation that was resolved within 3 days. This study does not satisfy guideline requirements (81-5) for a primary dermal irritation study. Upgrading is possible, however, upon the submission and favorable review of chemical analytical data establishing purity of the test article at the time of animal treatment. Toxicity Category IV.

Reviewed by: Walter J. Kozumbo, Ph.D. Walter J. Kozumbo 2-10-92
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/11/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral/Rats (81-1)
CHEM. TOX. NO.:	257BB
MRID NUMBER:	417593-01
TEST MATERIAL:	K-TEA
STUDY NUMBER:	3236.1
TESTING FACILITY:	Springborn Laboratories, Inc. Life Sciences Division 553 North Broadway Spencerville, OH 45887
SPONSOR:	Griffin Corporation P.O. Box 1847 Valdosta, GA 31603-1847
TITLE OF REPORT:	Acute Oral Toxicity Study in Rats with K-TEA
AUTHORS:	R. E. Rush, B.A.
REPORT ISSUED:	December 14, 1990
CONCLUSIONS:	The acute oral LD50s were determined in male and female Sprague Dawley rats for K-TEA Technical. In dosing units of mg/kg, the LD50s (plus 95% confidence intervals) were 1170 (462-1879) for males, 1481 (352-2610) for females, and 1312 (781-1842) for both sexes combined. No chemical analytical data were provided to verify the purity of K-TEA upon initiation of this study.
TOXICITY CATEGORY:	III
CLASSIFICATION:	Supplementary --- This study does not satisfy guideline requirements (81-1) for an acute toxicity study. Upgrading is possible, however, upon the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of animal treatment.

I. MATERIALS

A. Test Material:

K-TEA is a triethanolamine complex of copper. It exists as a blue liquid at room temperature with a density of 1.17 g/ml. It was received on April 26, 1990, and stored at room temperature until initiation of the study on July 30, 1990. No chemical analytical data were provided to indicate the purity of test article as administered to the animals.

B. Test Animals:

The test animals were young male and female Sprague-Dawley rats obtained from Charles River Laboratories, Inc., Portage, Michigan. At the start of the study, males weighed between 219 and 276 g, and females between 196 and 241 g. Upon arrival, the rats were housed individually in suspended stainless steel cages in a room environmentally controlled for humidity (40-70%), temperature (64-79 °C) and light/dark cycle (12/12 h). They were acclimated for at least 5 days before beginning the study and were provided food (Agway Prolab Rodent Feed) and water ad libitum. Water was analyzed once a year for contaminants.

II. METHODS

Rats (5/dose/sex) were fasted overnight and then administered a single, undiluted, oral dose of K-TEA at 500, 750, 1000 or 5000 mg/kg. The appearance and behavior of animals were observed frequently on the day of treatment and once daily thereafter until the end of the study on day 15. Animals were inspected for mortality twice a day. Body weights were recorded at the start of the study and once per week until the end of the study. Gross necropsy was performed on all animals at time of death/sacrifice. LD50 calculations were made on males and females both separately and combined using the method of Miller and Tainter (Proc. Soc. Exp. Biol. Med., 57: 261-264, 1944).

III. RESULTS

All chemically induced deaths occurred within 5 days of treatment. In the case of both male and female rats, the four doses encompassed a range of treatment that resulted in no mortality at the lowest dose and total mortality at the highest (see attached Table 1, p. 10). The LD50s determined from these spectra of mortality were 1170 mg/kg for males, 1481 mg/kg for females, and 1312 mg/kg for the sexes combined. The 95% confidence intervals and slopes for each the LD50 curves can be found in the attached Table 1.

Clinical signs of toxicity were predominantly observed within the first 3 days after treatment and included breathing problems, urine and fecal staining, diminished activity, hairloss, wobbly gait, feces reduction, and the accumulation of dark material around eyes, mouth and nose. All animals surviving to the end of study experienced weight gains. Upon necropsy, gross pathology findings were observed primarily in animals dying before the end of study and were therefore chemically related. These findings included staining (blue and green), reddening and distending of the stomach, as well as mucoid contents and staining (blue and yellow-orange) of the trachea. Animals sacrificed upon termination of the study demonstrated no chemically related pathology.

IV. CONCLUSIONS

The acute oral LD50s were determined in male and female Sprague Dawley rats for K-TEA Technical. In dosing units of mg/kg, the LD50s (plus 95% confidence intervals) were 1170 (462-1879) for males, 1481 (352-2610) for females, and 1312 (781-1842) for both sexes combined. No chemical analytical data were provided to verify the purity of K-TEA upon initiation of this study.

V. TOXICITY CATEGORY: III

VI. CORE CLASSIFICATION: Supplementary --- This study does not satisfy guideline requirements (81-1) for an acute toxicity study. Upgrading is possible, however, upon the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of animal treatment.

Page 10 is not included in this copy.

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____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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Reviewed by: Walter J. Kozumbo, Ph.D. Walter J. Kozumbo 2-10-92
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Yiannakis M. Ioannou 2/11/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity/Rabbits (81-2)
CHEM. TOX. NO.:	257BB
MRID NUMBER:	417593-02
TEST MATERIAL:	K-TEA
STUDY NUMBER:	3236.2
TESTING FACILITY:	Springborn Laboratories, Inc. Life Sciences Division 553 North Broadway Spencerville, OH 45887
SPONSOR:	Griffin Corporation P.O. Box 1847 Valdosta, GA 31603-1847
TITLE OF REPORT:	Acute Dermal Toxicity Study in Rabbits with K-TEA
AUTHORS:	R. E. Rush, B.A.
REPORT ISSUED:	October 11, 1990
CONCLUSIONS:	The single topical application of a limit-test dose of K-TEA Technical (2000 mg/kg) to 5 male and 5 female New Zealand white rabbits for 24 h resulted in no observed deaths after 15 days. The acute dermal LD50 for K-TEA in rabbits was therefore determined to be > 2000 mg/kg. Skin irritation was observed at the site of application. No chemical analytical data were provided to verify the purity of K-TEA upon initiation of this study.
TOXICITY CATEGORY:	III
CLASSIFICATION:	Supplementary --- This study does not satisfy guideline requirements (81-2) for an acute dermal toxicity study. Upgrading is possible, however, upon the receipt and favorable review of analytical data verifying purity of test article at the time of animal treatment.

I. MATERIALS

A. Test Material:

K-TEA is a triethanolamine complex of copper. It exists as a blue liquid at room temperature with a density of 1.17 g/ml. It was received on April 26, 1990, and stored at room temperature until initiation of the study on July 5, 1990. No chemical analytical data were presented indicating the purity of test article when administered to the animals.

B. Test Animals:

The test animals were 5 young adult New Zealand white rabbits of each sex obtained from Mohican Valley Rabbitry, Loudonville, Ohio. At the start of the study, males weighed between 2530 and 2710 g, and females between 2457 and 2724 g. Upon arrival, the rabbits were housed individually in suspended stainless steel cages in a room environmentally controlled for humidity (40-60%), temperature (61-70 °F) and light/dark cycle (12/12 h). They were acclimated for at least 5 days before beginning the study and were provided food (Agway Prolab Rabbit Feed) and water ad libitum. Water was analyzed once a year for contaminants.

II. METHODS

A day before dosing, the hair from the dorsal area of the trunk of 10 rabbits (5/sex) was removed with clippers. The test article was applied uniformly to the skin at a single limit-test dose of 2000 mg/kg over the clipped area. The application was covered with a gauze patch and then with a plastic wrap and a tubular sleeve held in place by tape. After a treatment period of 24 h, all coverings were removed and the remaining test article was washed away with distilled water. The appearance and behavior of animals were observed frequently on the day of treatment and once daily thereafter until the end of the study on day 15. Animals were inspected for mortality twice a day. Body weights were recorded on days 1, 8 and 15 of the study. Gross necropsy was performed on all animals at time of death/sacrifice.

III. RESULTS

No deaths occurred during the 15-day study period. Clinical signs of toxicity were limited to skin irritation at the application site. This consisted of edema (severe to slight), erythema (moderate to slight), eschar (multi-focal), and exfoliation. All animals gained weight during the course of the study. No indications of gross pathology were observed in any of the 10 animals sacrificed on day 15.

GLP/QA statements were signed and attached to the submitted study report.

IV. CONCLUSIONS

The single topical application of a limit-test dose of K-TEA Technical (2000 mg/kg) to 5 male and 5 female New Zealand white rabbits for 24 h resulted in no observed deaths after 15 days. The acute dermal LD50 for K-TEA in rabbits was therefore determined to be > 2000 mg/kg. Skin irritation was observed at the site of application. No chemical analytical data were provided to verify the purity of K-TEA upon initiation of this study.

V. TOXICITY CATEGORY: III

VI. CLASSIFICATION: Supplementary --- This study does not satisfy guideline requirements (81-2) for an acute dermal toxicity study. Upgrading is possible, however, upon the receipt and favorable review of analytical data verifying purity of test article at the time of animal treatment.

Reviewed by: Walter J. Kozumbo, Ph.D. Walter J. Kozumbo 2-10-92[1]
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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/11/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation/Rabbits (81-4)
CHEM. TOX. NO.:	257BB
MRID NUMBER:	417593-03
TEST MATERIAL:	K-TEA
STUDY NUMBER:	3236.3
TESTING FACILITY:	Springborn Laboratories, Inc. Life Sciences Division 553 North Broadway Spencerville, OH 45887
SPONSOR:	Griffin Corporation P.O. Box 1847 Valdosta, GA 31603-1847
TITLE OF REPORT:	Primary Eye Irritation Study in Rabbits with K-TEA
AUTHORS:	R. E. Rush, B.A.
REPORT ISSUED:	September 24, 1990
CONCLUSIONS:	In rabbits, K-TEA Technical produced moderate eye irritation involving "positive" effects on the cornea, iris and conjunctiva. Effects on the cornea and iris were completely resolved in 1 day while conjunctival redness diminished to a "non-positive" (barely perceptible) level of irritation within 7 days.
TOXICITY CATEGORY:	III
CLASSIFICATION:	Supplementary --- This study does not satisfy guideline requirements (81-4) for a primary eye irritation study. Upgrading is possible, however, on the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of animal treatment.

I. MATERIALS

A. Test Material:

K-TEA is a triethanolamine complex of copper. It exists as a blue liquid at room temperature with a density of 1.17 g/ml. It was received on April 26, 1990, and stored at room temperature until initiation of the study on July 9 1990. No chemical analytical data were provided to indicate the purity of test article at the time of administration to animals.

B. Test Animals:

The test animals were 6 adult New Zealand white rabbits obtained from Mohican Valley Rabbitry, Loudonville, Ohio. At the start of the ocular study, the rabbits weighed between 2.7 and 3.4 kg. The animals were housed individually in suspended stainless steel cages in a room environmentally controlled for humidity (40-60%), temperature (61-70 °F) and light/dark cycle (12/12 h). They were acclimated for at least 5 days prior to beginning the study and were provided food (Agway Prolab Rabbit Feed) and water ad libitum. Water was analyzed once a year for contaminants.

II. METHODS

The eyes of the rabbits were examined prior to the study using a fluorescein dye and long wave UV light. The corneas and irises were found to have no pre-existing abnormalities or irritation. K-TEA Technical (0.1 ml) was instilled under the lower eyelid of one eye into the conjunctival sac of each animal. The other eye of the animal was untreated and served as negative control.

The eyes were examined macroscopically at 1 h post instillation and daily for 3 days and up to 14 days after treatment. At the 24-h time point, the eyes were also examined for positive retention of fluorescein dye. Fluorescein examinations were continued at each ensuing interval until a negative response was observed. Eye irritation was scored numerically using an ocular irritation index (see attached 10 & 11). For each time point, the mean irritation score was calculated for each animal. For evaluation criteria see attached p. 12. At the end of the study, all animals were sacrificed with an euthanasia solution T-61®.

III. RESULTS

At the 1-h interval, a treatment-related sloughing of the corneal epithelia was observed in all 6 rabbits, with 2 of the animals showing some indications of a dulling in the normal

corneal luster (see attached pp. 13 & 14). Corneal opacity was, however, not observed. In 4 of the 6 animals, iritis was observed at the 1-h time point and resolved by 24 h. Redness, swelling and discharge were observed in the conjunctivae of the treated eyes. These effects were resolved from 1 to 14 days following treatment. By day 7, however, all effects designated as "positive" were resolved. No irritation effects were observed in non-treated eyes.

GLP/QA statements were signed and attached to the submitted study report.

IV. CONCLUSIONS

In rabbits, K-TEA Technical produced moderate eye irritation involving "positive" effects on the cornea, iris and conjunctiva. Effects on the cornea and iris were completely resolved in 1 day while conjunctival redness diminished to a "non-positive" (barely perceptible) level of irritation within 7 days.

V. TOXICITY CATEGORY: III

VI. CORE CLASSIFICATION: Supplementary --- This study does not satisfy guideline requirements (81-4) for a primary eye irritation study. Upgrading is possible, however, on the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of animal treatment.

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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/11/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation/Rabbits (81-5)
CHEM. TOX. NO.:	257BB
MRID NUMBER:	417593-04
TEST MATERIAL:	K-TEA
STUDY NUMBER:	3236.4
TESTING FACILITY:	Springborn Laboratories, Inc. Life Sciences Division 553 North Broadway Spencerville, OH 45887
SPONSOR:	Griffin Corporation P.O. Box 1847 Valdosta, GA 31603-1847
TITLE OF REPORT:	Acute Dermal Toxicity Study in Rabbits with K-TEA
AUTHORS:	R. E. Rush, B.A.
REPORT ISSUED:	October 11, 1990
CONCLUSIONS:	The single topical application of K-TEA Technical (0.5 ml) to 6 New Zealand white rabbits for 4 h produced only slight redness of the skin (score=1) that was completely resolved by 72 h. The purity of K-TEA upon initiation of this study was not indicated.
TOXICITY CATEGORY:	IV
CLASSIFICATION:	Supplementary --- This study does not satisfy guideline requirements (81-5) for a primary dermal irritation study. Upgrading is possible, however, upon the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of treatment.

I. MATERIALS

A. Test Material:

K-TEA is a triethanolamine complex of copper. It exists as a blue liquid at room temperature with a density of 1.17 g/ml. It was received on April 26, 1990, and stored at room temperature until initiation of the study on July 5, 1990. No chemical analytical data were presented indicating the purity of test article when administered to the animals.

B. Test Animals:

The test animals were 6 young adult New Zealand white rabbits of each sex obtained from Mohican Valley Rabbitry, Loudonville, Ohio. At the start of the study, males weighed between 2530 and 2710 g, and females between 2457 and 2724 g. Upon arrival, the rabbits were housed individually in suspended stainless steel cages in a room environmentally controlled for humidity (40-60%), temperature (61-70 °F) and light/dark cycle (12/12 h). They were acclimated for at least 5 days before beginning the study and were provided food (Agway Prolab Rabbit Feed) and water ad libitum. Water was analyzed once a year for contaminants.

II. METHODS

A day before dosing, the hair from the dorsal area of the trunk of 6 rabbits was removed with clippers. A volume of 0.5 ml of test article was applied uniformly to an area of skin measuring approximately 1 inch x 1 inch. The application was covered with a gauze patch, secured with non-irritating tape and then held in place by a tubular body sleeve. After a treatment period of 4 h, all coverings were removed and the remaining test article was washed away with distilled water. Animals were inspected at 1, 24, 48 and 72 h for erythema and edema occurring at the test sites. A Dermal Irritation Grading System (see attached p. 10) was used to score numerically the intensity of the irritation response. Animals were sacrificed by euthanasia solution T-61® at the end of the study. The Primary Irritation Index was determined by adding all scores from the 4 time points for each of the 6 animals and dividing by 24 (4 x 6) (see attached p. 11).

III. RESULTS

All animals survived treatment. Five of the 6 animals experienced barely perceptible redness (score=1) at the 1-h interval that was resolved in 4 of these animals within 24 h. The erythema in the fifth animal was gone by 72 h. The sixth animal showed no signs of erythema. None of the 6 animals showed any indications of edema (see attached p. 11).

GLP/QA statements were signed and attached to the submitted study report.

IV. CONCLUSIONS

The single topical application of K-TEA Technical (0.5 ml) to 6 New Zealand white rabbits for 4 h produced only slight redness of the skin (score=1) that was completely resolved by 72 h. The purity of K-TEA upon initiation of this study was not indicated.

V. TOXICITY CATEGORY: IV

VI. CORE CLASSIFICATION: Supplementary --- This study does not satisfy guideline requirements (81-5) for a primary dermal irritation study. Upgrading is possible, however, upon the receipt and favorable evaluation of chemical analytical data verifying purity of test article at the time of treatment.

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